OPINION

Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia

Bryan L. Roth, Douglas J. Sheffler and Wesley K. Kroeze

Most common central nervous system disorders — such as depression, bipolar disorder and schizophrenia — seem to be polygenic in origin, and the most effective medications have exceedingly complex pharmacologies. Attempts to develop more effective treatments for diseases such as schizophrenia and depression by discovering drugs selective for single molecular targets (that is, 'magic bullets') have, not surprisingly, been largely unsuccessful. Here we propose that designing selectively non-selective drugs (that is, 'magic shotguns') that interact with several molecular targets will lead to new and more effective medications for a variety of central nervous system disorders.

Despite their enormous potential to alleviate human suffering, before the introduction of fluoxetine (Prozac; Eli Lilly) in the late 1980s central nervous system (CNS) therapeutics were not widely embraced as either highly reliable or profitable. This is despite the fact that from the 1960s to the 1970s selected areas of CNS drug discovery yielded profitable drugs (for example, Valium, Milltown and Haldol). This was due, in part, to the lack of suitable animal models, disagreements regarding the biological basis of many disorders, uncertainty regarding the ultimate mechanism(s) of action and the clinical ineffectiveness of many CNS medications[1]. During the past two decades, CNS drug discovery — particularly in the areas of mood disorders and schizophrenia — has become one of the most profitable sectors of the pharmaceutical market. CNS drugs account for 11 of the top 25 drugs on the US market, with annual US sales in excess of US $17 billion (2002 sales figures). Additionally, it is now widely accepted that moderately effective treatments exist for most of the common CNS diseases, including schizophrenia, depression, anxiety disorders, insomnia, migraine headaches, chronic pain and seizure disorders. This article will focus on the two largest sectors of the CNS drug market: atypical antipsychotic drugs for schizophrenia and related disorders, and antidepressants for depression and anxiety disorders.

Despite the acknowledged potential of CNS therapeutic agents, few drugs with truly novel mechanisms of action have been introduced in the past several decades. Indeed, the most widely prescribed drugs — the serotonin-selective reuptake inhibitors (SSRIs) and atypical antipsychotic drugs — represent only marginal advances over the prototypes zimelidine (discovered in 1971 (REF. 2)) and clozapine (discovered in 1958 (REF. 3)).

Because the aetiology of depression and schizophrenia is unknown, choosing the appropriate molecular target for drug discovery is especially risky. In terms of aetiology, it is now widely accepted that the major mental illnesses are polygenic[4,5], with substantial environmental and, perhaps, epigenetic components. The polygenic and non-genetic components of major CNS diseases makes the use of genetically engineered mice to provide validated models for drug discovery efforts precarious[6].

Another fundamental difficulty with developing novel CNS therapeutics is the appreciation that the most widely prescribed CNS medications, especially those for mood disorders (for example, lithium, anticonvulsants and antidepressants[7]) and schizophrenia[8] have complex and ill-defined mechanisms of action. As will be summarized below, the discovery that the most clinically effective CNS drugs are pharmacologically complex, with pleiotypic actions (that is, they act as 'magic shotguns'), has made the development of 'magic bullets' (that is, drugs selective for a single molecular target) less likely.

Why 'dirty' drugs might be better

Even though clozapine was discovered nearly 50 years ago[3], it remains the 'gold standard' atypical antipsychotic drug because of the absence of debilitating extra-pyramidal side-effects and demonstrated clinical superiority in treating schizophrenia[9] and in reducing suicidality[10]. However, clozapine is also associated with severe and potentially life-threatening side effects, including an increased risk of agranulocytosis, seizures, weight gain and diabetes, and is therefore typically prescribed only for individuals with 'treatment-resistant' schizophrenia. Clozapine has a highly complex pharmacological profile, with high affinity for a number of serotonin (5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), dopamine (D_4), muscarinic (M_1, M_2, M_3, M_4, M_5), adrenergic (α_1- and α_2-subtypes) and other biogenic amine receptors (REF. 8 and references cited therein).

FIGURE 1 shows the distribution of some of the receptors targeted by clozapine in relation to various molecular targets implicated by genetic studies of schizophrenia (see REFS 4,5 for details). As can be seen in FIG. 1, many of the genes implicated in the aetiology of schizophrenia are found in anatomical loci where they could, directly or indirectly, modulate glutamatergic and dopaminergic neurotransmission in the frontal cortex. Clozapine is

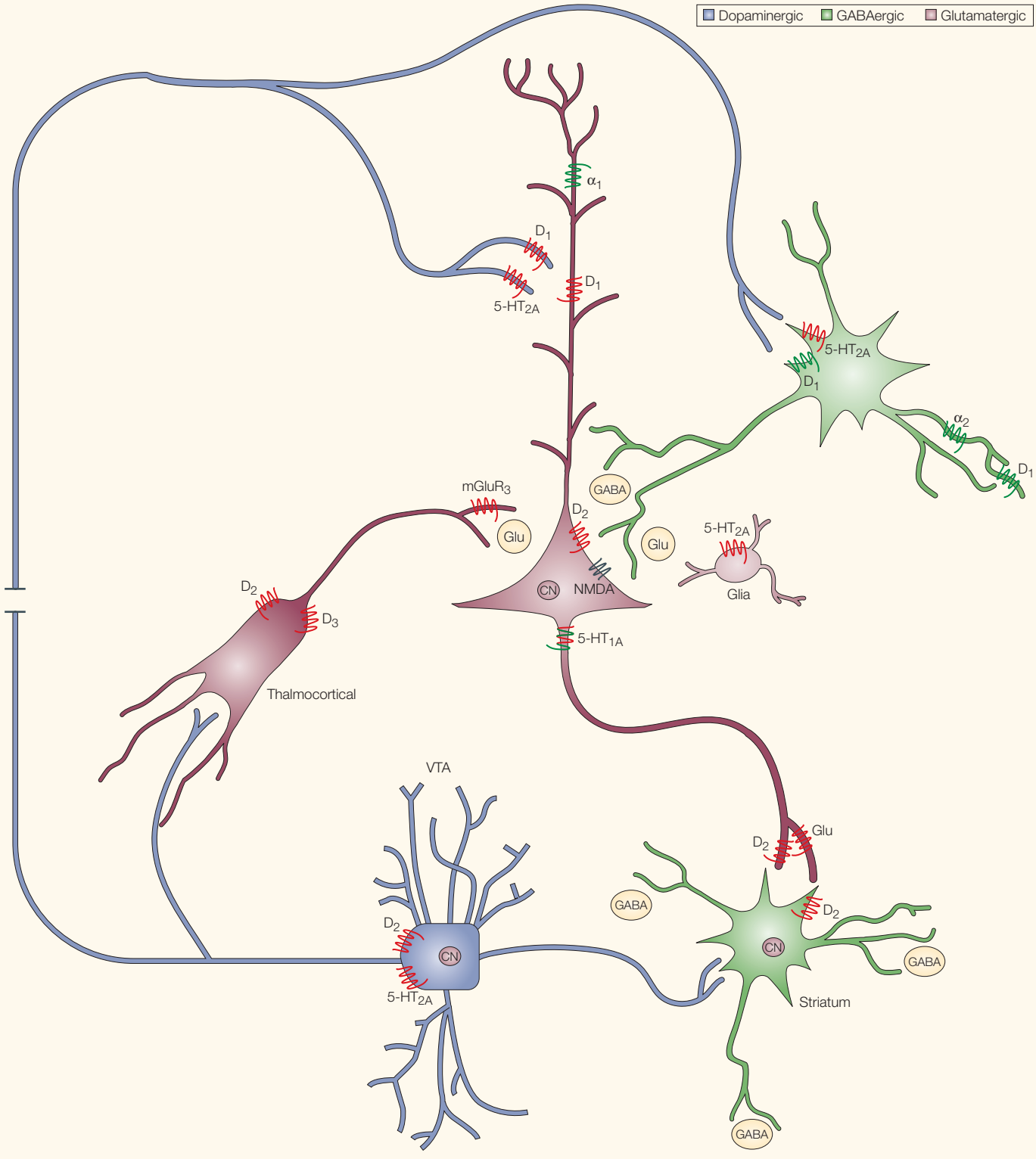


Figure 1 | **Neuronal circuits implicated in schizophrenia aetiology and treatment.** Shown is a schematic diagram of the wiring of the frontal cortex, emphasizing inputs into cortical glutamatergic pyramidal neurons. Some of the various molecular targets implicated as risk factors for schizophrenia are shown, including calcineurin (CN) γ-subunit, the D_1- and D_3-dopamine receptors (D_1, D_3) and metabotrophic glutamate receptor 3 (mGluR3). Other molecular targets not shown include catechol-*O*-methyltransferase, reelin, dysbindin, regulator of G-protein signalling-4 and neuregulin (see REFS 4,5 and references cited therein). Receptors at which clozapine is an antagonist are depicted in red and those at which clozapine is a partial agonist are shown in green (see REF. 8 and references cited therein) and include the following: 5-HT_{1A}- and 5-HT_{2A}-serotonin, D_1-, D_2- and D_3-dopamine, α_1- and α_2-adrenoceptors. For the purposes of clarity, not all of the various molecular targets implicated as risk factors for schizophrenia or those occupied by clozapine are shown. For the sake of simplicity, many other neuronal and biochemical interactions are omitted. GABA, γ-aminobutyric acid; GLU, glutamate; mGluR3, metabotrophic glutamate receptor 3; NMDA, *N*-methyl-D-aspartate; VTA, ventral tegmental dopamine neuron.

thought to normalize glutamatergic and dopaminergic neurotransmission in schizophrenia, thereby ameliorating symptoms, via complex interactions with a large number of molecular targets (FIGS 1,2). These pleiotypic actions of clozapine are probably responsible for its exceptionally beneficial actions in schizophrenia and related disorders[9,10].

A graphical representation of the relative affinity values of clozapine and a number of other atypical antipsychotic drugs (aripiprazole, ziprasidone, zotepine, quetiapine, olanzapine, risperidone) and typical antipsychotic drugs (haloperidol, chlorpromazine) at a portion of the receptorome (that is, that portion of the proteome comprising receptors) is shown in FIG. 2. As can be seen, most of the presently approved atypical antipsychotic drugs have a complex pharmacology, with appreciable affinities for a variety of biogenic amine receptors. Given the huge potential market for atypical antipsychotic drugs (~US $10 billion annually), great effort has been devoted to uncovering the receptors responsible for effectiveness, for atypicality and for side effects. The idea has been that if one could design drugs that targeted the appropriate receptors, one could develop atypical antipsychotic drugs that are more effective than clozapine and have fewer side effects. These efforts will be furthered in the future by the precise delineation of the areas of the brain in which the drug exerts its beneficial effects, as well as characterization of the intracellular biochemical pathways contributing to both effectiveness and the development of side effects.

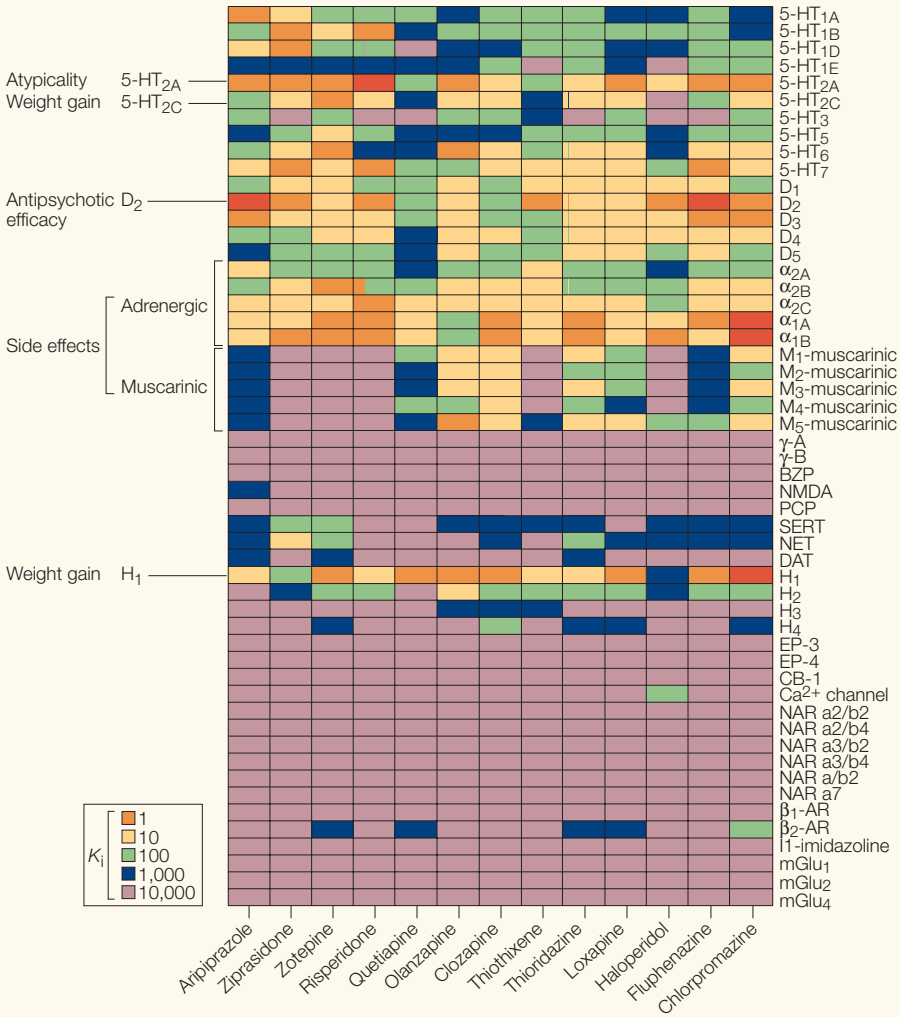


Figure 2 | **Screening the receptorome reveals multiple molecular targets implicated in antipsychotic drug actions.** The affinity (K_i) values for clozapine and a large number of other biologically active compounds at various receptors can be found at the PDSP K_i Database (see Further Information); the database is part of the National Institute of Mental Health Psychoactive Drug Screening Program (see Further Information) and represents the largest database of its kind in the public domain. At present, the PDSP K_i database has >26,000 K_i values for more than 300 receptors.

'S_2/D_2' drugs: not quite clozapine

The first 'non-clozapine' atypical to be marketed was risperidone, which potently blocks the effects of lysergic acid diethylamide (LSD) in laboratory animals by virtue of its high affinity for 5-HT_{2A} receptors[11]. A systematic analysis of receptor pharmacology of a number of typical and atypical antipsychotic drugs led Meltzer[12] and others[13] to propose that the single distinguishing feature of an atypical antipsychotic drug was a relatively high affinity for 5-HT_{2A} relative to D_2 receptors (the 'S_2/D_2 hypothesis of atypicality'). Subsequently, several atypical antipsychotic drugs were introduced that fulfilled the 'S_2/D_2' criterion, including olanzapine, ziprasidone, zotepine and quetiapine. Although these drugs represent an advance in the treatment of schizophrenia, none of the presently approved atypical antipsychotic drugs is better than clozapine for schizophrenia[14,15]. As a class, the 'S_2/D_2 atypicals' are not without serious side effects, including weight gain and the associated metabolic sequelae of diabetes and hypercholesterolaemia[16]. In this regard, recent studies have implicated the histamine receptor H_1, the 5-HT_{2C} receptor and α_1-adrenoceptors — sites for which many atypical antipsychotic drugs have high affinity — for causing weight gain and associated metabolic side effects[17]. S_2/D_2 atypicals that have relatively low affinity for H_1 receptor and α_1-adrenoceptors (for example, ziprasidone) are less likely to induce weight gain. Because other CNS medications that induce weight gain, such as amitryptiline, mirtazepine and imipramine (see PDSP K_i Database, Further Information), also have high H_1, 5-HT_{2C}- and α_1-adrenoceptor affinities, these data strongly imply that antipsychotic drugs that lack affinities at H_1, 5-HT_{2C} and α_1 receptors will be less likely to induce the metabolic side effects of many of the presently marketed drugs.

In addition to improving the core symptoms of schizophrenia, such as hallucinations and delusions, atypical antipsychotic drugs as a class modestly improve cognition[18], though it is unknown how these cognition-enhancing actions are mediated. Current hypotheses suggest that the cognition-enhancing actions of atypicals may be due to interactions with 5-HT_{2A}[19] and 5-HT_6[20] receptors, and to their abilities to enhance prefrontal cortical dopamine release[21] (FIG. 1).

Many attempts, largely unsuccessful, have been made to develop drugs that target the 'magic receptor' responsible for clozapine's salutary effects in schizophrenia and related disorders and, thereby, yield novel atypical antipsychotic drugs. For instance, D_4-selective compounds[22], as well as compounds with 5-HT_{2A}/D_4 antagonism[23], are ineffective in

Table 1 | **Non-D_2 dopamine antagonists in schizophrenia are inferior**

Receptor	Representative compound	Results versus placebo	Results versus comparator	References
5-HT_{2A}	M100907	Better	Worse	
5-$HT_{2A/2C}$	SR46349B	Better	Similar	25
5-HT_6	SB271046	In Phase I	NA	*see footnote
5-HT_{2A}/D_4	Fananserin	Potentially worse or similar to placebo	NA	23
D_2-dopamine partial agonist	(–)PPP	Worse with moderate efficacy	NA	28
D_3-dopamine partial agonist	(+)-UH232	Worse	NA	29
D_3-dopamine	SB-277011	In trials	NA	52
D_4-dopamine	L-745,870	Potentially worse or similar to placebo	NA	53
CB_1 cannabinoid	SR-141716	Worse	Worse	25
Sigma	BMY-14802	Similar to placebo	NA	54
Sigma	Panamesine	Better (small trial)	NA	55
NK_3	SR142801	Better	Same	25
NT_1	SR48692	Worse	Worse	25
Glutamate	D-cycloserine	Similar to placebo with marginal effect on negative symptoms; may augment actions of atypical antipsychotic drugs	NA	56,57

* See http://science.gsk.com/pipeline/pipeline2002oct.pdf for details. 5-HT, serotonin; NK, neurokinin; NT, neurotensin.

treating schizophrenia. Likewise, the 5-HT_{2A} selective compound M100907 (REF. 24) failed to reduce symptoms to the same extent as haloperidol (a typical antipsychotic drug comparator) in a multi-centre clinical trial, whereas the 5-$HT_{2A/2C}$ antagonist SR46349B fared better in comparison with haloperidol[25] (TABLE 1). There have also been suggestions that compounds with muscarinic[26] or adrenoceptors (both α_2- and α_1-adrenoceptors) actions might be effective antipsychotic drugs but, so far, none have shown efficacy in clinical trials (see REF. 8 and references cited therein). TABLE 1 lists a number of other 'magic bullets' which, with few exceptions, were shown to lack efficacy in schizophrenia.

Partial agonists for schizophrenia

Some years ago, Carlsson proposed that (–)-3-(3-hydroxyphenyl)-*N*-n-propylpiperidine ((–)PPP), by virtue of its autoreceptor agonist properties, might represent a prototype for a new family of atypical antipsychotic drugs[27]. Carlsson's notion was that a partial agonist would normalize or 'stabilize' dopaminergic neurotransmission in a way that would be salutary for both the positive and negative symptoms of schizophrenia. Two potential compounds were subsequently tested: (–)PPP and (+)-UH232 (a D_3-preferring agonist with 5-HT_{2A} agonism). When (–)PPP was tested in schizophrenia, it was found to be effective for a short period (~one week), after which clinical efficacy was lost — presumably due to receptor desensitization[28]. Because (–)PPP has substantial affinities for non-D_2 receptors (for example, σ-, α_{2B}- or α_{2C}-adrenoceptors; see PDSP Database, Further Information), it is conceivable that the ineffectiveness of (–)PPP was due to unforeseen interaction with non-D_2 receptors. Intriguingly, (+)-UH232 actually worsened psychotic symptoms, perhaps via a combination of D_3 and 5-HT_{2A} agonism[29], because 5-HT_{2A} agonism is known to exacerbate psychosis[62].

On the basis of these early trials, it was unclear whether (–)PPP's lack of efficacy beyond one week was due to either inadvertent interaction with psychotomimetic receptors (for example, σ_1-adrenoceptor) or the relatively high intrinsic activity of (–)PPP leading to desensitization. Several other D_2 partial agonists, including terguride, OPC-4392, pramipexole and SDZ HDC 912, have now been tested in schizophrenia, mainly unsuccessfully[30]. To date, only aripiprazole (OPC 14597), a weak D_2 partial agonist[31], has shown efficacy for schizophrenia[32], although considerable controversy exists regarding its mechanism of action (BOX 1).

Kikuchi *et al.*[31] originally proposed that aripiprazole was a presynaptic agonist and a postsynaptic antagonist and would therefore 'stabilize' dopaminergic neurotransmission. This notion of 'anatomical selectivity' is difficult to reconcile with later findings that aripiprazole is a D_2 partial agonist at postsynaptic pituitary D_2 receptors *in vitro* and *in vivo*[33]. Likewise, the D_2 partial agonism has been inconsistently replicated, with some groups reporting that aripiprazole is a high-affinity partial agonist *in vitro*[34], and others reporting that aripiprazole is a D_2 antagonist *in vivo* and *in vitro*[35]. By contrast, Lawler *et al.*[36] proposed that aripiprazole was 'functionally selective' and that the agonist properties of aripiprazole were entirely dependent on the cellular milieu in which it was studied. As a result, it was proposed[36] that aripiprazole might function as a D_2 antagonist, agonist or partial agonist depending on the precise complement of D_2 receptors and G-proteins in a particular cell. This notion is similar to the idea of agonist-directed trafficking of receptors (see REF. 37 for a recent review), an idea originally proposed many years ago[38]. This idea proposes that receptors can couple to several signal transducing molecules and suggests that "selective agonists and antagonists might be developed which have specific effects on a particular receptor-linked effector system."[38]

When the various competing hypotheses of aripiprazole's actions were tested, we found[39], in support of the hypothesis of Lawler *et al.*[36], that the actions of aripiprazole were entirely dependent on the cellular milieu. Interestingly, we also discovered[39] that aripiprazole had a robust pharmacological profile with partial agonism at several 5-HT (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_7) and dopamine (D_2, D_3, D_4) receptors. So although aripiprazole is clearly a functionally selective partial agonist, its complex pharmacology precludes us from concluding that its beneficial actions in schizophrenia are due solely to partial agonism of D_2 receptors. It is more likely that the balance of partial agonism and antagonism at a multiplicity of receptors is responsible for its efficacy in schizophrenia and related disorders. Taken together, these findings have profound implications for CNS drug discovery, because they imply that simply developing selective low-efficacy D_2 partial agonists will not yield effective antipsychotic drugs, but that D_2 partial agonists that functionally interact with various 5-HT and dopamine receptors might be effective. Therefore functionally non-selective dopamine agonists might represent a new generation of atypical antipsychotic drugs, with aripiprazole being the first member of this class.

Non-selective antidepressants?

If 'dirty' drugs are better for treating schizophrenia than selective ('clean') ones, what about other CNS disorders? TABLE 2 lists the current classes of antidepressants, ranking them by their relative effectiveness in treating depression. The most effective treatment for depression — electroconvulsive therapy (ECT) — alters the dynamics of a vast number of neurotransmitters and neuromodulators, and has profound effects on intracellular signalling pathways related to signal transduction and mitogenesis[7]. Indeed, very recent studies imply that the pleiotypic actions of antidepressants on signal transduction and neuronal mitogenesis are required for the beneficial actions of antidepressants on mood[40]. Likewise, so-called 'dual-action' antidepressants, which inhibit the reuptake of both 5-HT and other biogenic amines (for example, dopamine and noradrenaline), have been shown to be more effective than 'single-action' antidepressants such as the SSRIs[41,42]. As an added benefit, the 'dual-action' antidepressants also seem to effectively treat chronic pain[43]. Finally, recent genetic studies have implied that depression, like schizophrenia, is a complex disorder with linkage to several genes[44] , including many that converge on the transcription factor cAMP-responsive element binding protein-1 (CREB1). These results imply that improved treatments for mood disorders are likely to arise from drugs with several mechanisms of action, and that studies that connect new knowledge of genetic linkage of these diseases in humans with those of changes in gene regulation in disease, as well as after treatment, are likely to be helpful in the development of new therapies.

Implications for CNS drug discovery

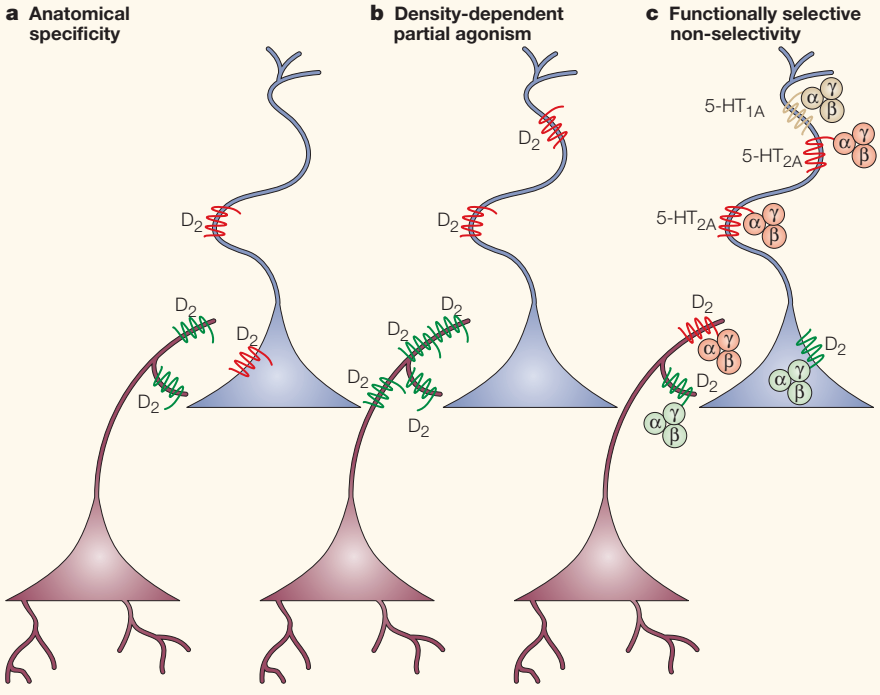
Given that selectively non-selective drugs are likely to be more beneficial than single-action agents in many CNS disorders, how best to develop them? Clearly, conventional approaches relying on high-throughput screening (HTS) of cloned human molecular targets and the subsequent optimization of these 'single-target agents' is not likely to yield selectively non-selective agents, except, perhaps, by chance. Structure-based drug design approaches in which ligands are designed to interact with the correct subset of molecular targets are also not likely to be successful. This is because many of the molecular targets selected have a high degree of structural similarity and designing drugs to target a subset of them is not likely to be successful (see REF. 63 for discussion).

The implication of these findings is that the screening of small molecules by non-conventional approaches should be considered. Conceptually, at least two non-conventional approaches for discovering 'magic shotguns' can be envisioned: behaviour-based screening and genomic approaches. The first, which has been dubbed 'HTS'-based behavioural screening'[45,46], relies on the semi-automated screening of candidate drugs in broad-based behavioural assays. At least two novel antidepressants — YKP10A and INN 00835 — were discovered using this approach. Neither drug seems to have appreciable affinity for any known antidepressant drug target, including various biogenic amine receptors and transporters[47], and both have demonstrated effectiveness in early-phase trials[48,47]. It is probable that the large-scale, automated and random screening of libraries of compounds enriched for activity at CNS targets, using mainly behavioural assays, will yield compounds with novel and, possibly improved, efficacies for a variety of CNS diseases. These approaches carry with them the advantage of examining responses to drugs at the level of entire organisms, and therefore in the context of their biological functioning, rather than in overly simplified experimental systems, for example, as in isolated *in vitro* binding studies.

Another approach is a genomic one in which compounds are screened solely on the basis of their abilities to modify the

Box 1 | **Partial functionally selective agonists for schizophrenia?**

The figure shows three different proposed models of aripiprazole action. In these various models, receptors coloured green are activated by aripiprazole and those coloured red are antagonized; receptors colourd yellow can be partially activated by aripiprazole, depending on the assay conditions. In panel a, the anatomical specificity model is highlighted. This model originally proposed that partial agonists which are effective in treating schizophrenia have differential actions at pre- and postsynaptic D_2 dopamine receptors[31]. This model proposed that aripiprazole, for instance, is a presynaptic agonist and a postsynaptic antagonist; these dual actions thereby 'normalize' dopaminergic signalling. In panel b, the density-dependent partial agonist model[34] is shown schematically. This model, which relies on classical receptor theory, proposes that aripiprazole is a partial agonist whose actions depend solely on the relative density of D_2-dopamine receptors. As such, in brain regions in which relatively high concentrations of D_2-dopamine receptors exist, drugs like aripiprazole would be partial agonists, whereas in brain regions with relatively low concentrations of D_2 receptors exist aripiprazole would function as an antagonist. In panel c, we show our conceptualization of the functional selectivity model. This model proposes that aripiprazole's partial agonist actions at a variety of G-protein-coupled receptors (GPCRs) are dependent on the precise cellular complement of receptors and G-proteins[36] and relies on our current understanding of GPCR actions. This model predicts that partial agonists, such as aripiprazole, will have a multiplicity of actions, functioning as agonists, partial agonists or antagonists. Indeed, recent studies indicate that the functional selectivity model best explains aripiprazole's actions[39].



coordinated expression of gene families. In this approach, compounds with known beneficial actions and pleiotypic actions (for example, lithium, clozapine) are screened *in vivo* and *in vitro* for their effects on coordinated gene expression. Once gene 'signatures' are discovered, compound libraries are subsequently screened to discover small molecules which, when administered *in vitro* and *in vivo*, yield similar signatures; such an approach is now being undertaken by Psychiatric Genomics, Inc.[49]. Lead compounds can then be optimized to eliminate interactions with potentially toxic molecular targets (for example, H_1 receptor for weight gain[17], human ether-a-go-go-related gene K^+ channel for arrhythmias[50] and the 5-HT_{2B} receptor for fenfluramine-like valvular heart disease[51]). In addition, it might prove possible to use combinations of compounds to 'fine-tune' these gene regulatory signatures.

The end of serendipity?

Historically, serendipity has been the driving force in the discovery of novel and highly effective drugs for CNS disorders. Not surprisingly, the most clinically effective treatments for depression and schizophrenia, and perhaps other disorders, continue to be the ones with the most nonspecific actions. It is likely that selectively non-selective drugs — 'magic shotguns' — could be discovered by combining behavioural and genomics-based screening. Once leads are discovered, potential toxicities could be relatively easily 'designed out' by counter-screening approaches combined with straight-forward medicinal chemistry approaches. Such magic shotguns, or selectively non-selective drugs, are likely to represent highly effective and novel treatments for major CNS disorders. The rational discovery, optimization and eventual marketing of selectively non-selective drugs will end our reliance on serendipity as the driving force for effective drug discovery for CNS disorders. On the other hand, in a

Table 2 | **Antidepressants with complex modes of action are superior to single-action antidepressants**

Prototypical drug	Class	Mode*	Molecular target(s)	Phase of testing	Efficacy vs SSRI	Company
Electro-convulsive therapy	Somatic therapy	C	Undefined	In use for decades	Greater efficacy[58]	None
Imipramine	Tricyclic antidepressant	C	NET, SERT, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, α_1-adrenergic, muscarinic	In use for decades	Slight advantage[41]	Generic
Fluoxetine	Serotonin-selective reuptake inhibitor	S	SERT	In use for >10 years	N/A	Eli Lilly
Venlafaxine	Dual serotonin/ norepinephrine reuptake inhibitor	C	NET; SERT	In use 10 years	Slight advantage[41,42,59]	Wyeth
Pindolol	5-HT_{1A} partial agonist/SSRI combination	C	5-HT_{1A}	Several double-blind, placebo controlled clinical trials completed; both drugs approved for use	Combination > than SSRI alone in uncomplicated depression[60] but not in refractory or chronic depression[61]	Generic
Duloxetine	Dual serotonin/ norepinephrine reuptake inhibitor	C	NET; SERT	NDA submitted	Unknown; predicted to be >than SSRIs	Eli Lilly
Gepirone	5-HT_{1A} partial agonist	S	5-HT_{1A}	NDA submitted; several 5-HT_{1A} partial agonists have been previously tested as single agent treatments for depression with modest success	Unknown; predicted to be < or = to SSRIs	Glaxo Smith Kline
Memantine	NMDA antagonist	S	NR2B	NDA submitted for Alzheimer's; in use in Europe for decades; preclinical research suggests efficacy	Unknown; predicted to be < or = to SSRIs	Forrest
Aprepitant	NK1 antagonist	S	NK-1	Phase III favourable	Discontinued; marginally effective	Merck
Agomelatine	Melatonin/5-HT receptor antagonist	C	MT-1; 5-HT_{2B}; 5-HT_{2C}	Phase III favourable	Unknown; could be superior to SSRIs	Servier
Nemifitide (INN 00835)	Unknown	C‡	Unknown	Phase II/III favourable	Unknown; dropped from further testing due to toxicity	InnaPharma
SB 723620	CRF1	S	CRF1	Phase I	Unknown; predicted to be < or = to SSRIs	Glaxo Smith Kline
SNAP-7941	MCH-1	S	MCH-1	Preclinical	Unknown; predicted to be < or = to SSRIs	Synaptic Pharmaceuticals
YKP-10A	Unknown	C‡	Unknown	Phase II favourable	Unknown	SK Corporation

*C, complex mode of action; S, simple mode of action. ‡Presumed.

recent colloquium sponsored by the Collegium Internationale Neuro-Psychopharmacologicum, Arvid Carlsson has argued that the field of CNS drug discovery is likely to continue to depend very much on serendipity. The approaches he suggested to facilitate these serendipitous discoveries are very similar to those outlined above, although we would argue that the results of such searches will not be serendipitous at all, but rather the result of looking for the right thing (magic shotguns) in the right place and at the right time.

Bryan L. Roth, Douglas J. Sheffler and Wesley K. Kroeze are in the Department of Biochemistry, School of Medicine, Case Western Reserve University, 2109 Adelbert Road, Cleveland, Ohio 44106, USA.
Correspondence to B.L.R.
e-mail: bryan.roth@case.edu

doi:10.1038/nrd1346

1. Shorter, E. Looking backwards: a possible new path for drug discovery in psychopharmacology. *Nature Rev. Drug Discov.* **1**, 1003–1006 (2002).
2. Carlsson, A. & Wong, D. T. Correction: a note on the discovery of selective serotonin reuptake inhibitors. *Life Sci.* **61**, 1203 (1997).
3. Hippius, H. A historical perspective of clozapine. *J. Clin. Psychiatry* **60** (Suppl. 12), 22–23 (1999).
4. Harrison, P. J. & Owen, M. J. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* **361**, 417–419 (2003).
5. Lewis, C. M. *et al*. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *Am. J. Hum. Genet.* **73**, 34–48 (2003).
6. Setola, V. & Roth, B. L. Why mice are neither miniature humans nor small rats: a cautionary tale involving 5-hydroxytryptamine-6 serotonin receptor species variants. *Mol. Pharmacol.* **64**, 1277–1278 (2003).
7. Coyle, J. T. & Duman, R. S. Finding the intracellular signaling pathways affected by mood disorder treatments. *Neuron* **38**, 157–160 (2003).
8. Roth, B., Sheffler, D. J. & Potkin, S. Atypical antipsychotic drugs: unitary or multiple mechanisms for 'atypicality'. *Clin. Neurosci. Res.* (in the press).
9. Kane, J., Honigfield, G., Singer, J., Meltzer, H. Y. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch. Gen. Psychiatry* **45**, 789–796 (1988).
10. Meltzer, H. Y. *et al*. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch. Gen. Psychiatry* **60**, 82–91 (2003).
11. Colpaert, F. C. Discovering risperidone: the LSD model of psychopathology. *Nature Rev. Drug Discov.* **2**, 315–320 (2003).
12. Meltzer, H. Y., Matsubara, S. & Lee, J.-C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pK_i values. *J. Pharmacol. Exp. Ther.* **251**, 238–246 (1989).
13. Altar, C. A., Wasley, A. M., Neale, R. F. & Stone, G. A. Typical and atypical antipsychotic occupancy of D_2 and S_2 receptors: an autoradiographic analysis in rat brain. *Brain Res. Bull.* **16**, 517–525 (1986).
14. Leucht, S., Wahlbeck, K., Hamann, J. & Kissling, W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* **361**, 1581–1589 (2003).
15. Tuunainen, A., Wahlbeck, K. & Gilbody, S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. *Schizophr. Res.* **56**, 1–10 (2002).
16. Fontaine, K. R. *et al*. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. *Psychiatry Res.* **101**, 277–288 (2001).
17. Kroeze, W. K. *et al*. H_1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* **28**, 519–526 (2003).
18. Meltzer, H. Y. & McGurk, S. R. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr. Bull.* **25**, 233–255 (1999).
19. Williams, G. V., Rao, S. G. & Goldman-Rakic, P. S. The physiological role of 5-HT_{2A} receptors in working memory. *J. Neurosci.* **22**, 2843–2854 (2002).
20. Woolley, M. L., Bentley, J. C., Sleight, A. J., Marsden, C. A. & Fone, K. C. A role for 5-HT_6 receptors in retention of spatial learning in the Morris water maze. *Neuropharmacology* **41**, 210–219 (2001).
21. Castner, S. A., Williams, G. V. & Goldman-Rakic, P. S. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D_1 receptor stimulation. *Science* **287**, 2020–2022 (2000).
22. Bristow, L. J. *et al*. Schizophrenia and L-745,870, a novel dopamine D_4 receptor antagonist. *Trends Pharmacol. Sci.* **18**, 186 (1997).
23. Truffinet, P. *et al*. Placebo-controlled study of the D_4/5-HT_{2A} antagonist fananserin in the treatment of schizophrenia. *Am. J. Psychiatry* **156**, 419–425 (1999).
24. de Paulis, T. M-100907 (Aventis). *Curr. Opin. Investig. Drugs* **2**, 123–132 (2001).
25. Meltzer, H., Arvantis, L., Bauer, D., Rein, W. & Group, M. S. A placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Arch. Gen. Psychiatry* (in the press).
26. Rasmussen, T. *et al*. The muscarinic receptor agonist BuTAC, a novel potential antipsychotic, does not impair learning and memory in mouse passive avoidance. *Schizophr. Res.* **49**, 193–201 (2001).
27. Clark, D. *et al*. Is 3-PPP a potential antip sychotic agent? Evidence from animal behavioral studies. *Eur. J. Pharmacol.* **83**, 131–134 (1982).
28. Lahti, A. C. *et al*. Antipsychotic properties of the partial dopamine agonist (–)-3-(3-hydroxyphenyl)-*N*-n-propylpiperidine(preclamol) in schizophrenia. *Biol. Psychiatry* **43**, 2–11 (1998).
29. Lahti, A. C., Weiler, M., Carlsson, A. & Tamminga, C. A. Effects of the D_3 and autoreceptor-preferring dopamine antagonist (+)-UH232 in schizophrenia. *J. Neural Transm.* **105**, 719–734 (1998).
30. Benkert, O., Muller-Siecheneder, F. & Wetzel, H. Dopamine agonists in schizophrenia: a review. *Eur. Neuropsychopharmacol.* **5**, S43–S53 (1995).
31. Kikuchi, T. *et al*. 7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-qui nolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D_2 receptor antagonistic activity. *J. Pharmacol. Exp. Ther.* **274**, 329–336 (1995).
32. Kane, J. M. *et al*. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin. Psychiatry* **63**, 763–771 (2002).
33. Inoue, T., Domae, M., Yamada, K. & Furukawa, T. Effects of the novel antipsychotic agent 7-(4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597) on prolactin release from the rat anterior pituitary gland. *J. Pharmacol. Exp. Ther.* **277**, 137–143 (1996).
34. Burris, K. D. *et al*. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D_2 receptors. *J. Pharmacol. Exp. Ther.* **302**, 381–389 (2002).
35. Hemrick–Luecke, S. *et al*. Pharmacological activity of aripiprazole at presynaptic and postsynaptic dopamine receptors and in antipsychotic models. *Proc. Soc. Neurosci.* 894.9 (2002).
36. Lawler, C. P. *et al*. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* **20**, 612–627 (1999).
37. Kenakin, T. Efficacy at G-protein-coupled receptors. *Nature Rev. Drug Discov.* **1**, 103–110 (2002).
38. Roth, B. L. & Chuang, D. M. Multiple mechanisms of serotonergic signal transduction. *Life Sci.* **41**, 1051–1064 (1987).
39. Shapiro, D. A. *et al*. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* **28**, 1400–1411 (2003).
40. Santarelli, L. *et al*. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301**, 805–809 (2003).
41. Anderson, I. M. Meta-analytical studies on new antidepressants. *Br. Med. Bull.* **57**, 161–178 (2001).
42. Thase, M. E., Entsuah, A. R. & Rudolph, R. L. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br. J. Psychiatry* **178**, 234–241 (2001).
43. Briley, M. New hope in the treatment of painful symptoms in depression. *Curr. Opin. Investig. Drugs* **4**, 42–45 (2003).
44. Zubenko, G. *et al*. Genome-wide linkage survey for genetic loci that influence the development of depressive disorders in families with recurrent, early-onset, major depression. *Am. J. Med Genet.* **123B**, 1–18 (2003).
45. Brunner, D., Nestler, E. & Leahy, E. In need of high-throughput behavioral systems. *Drug Discov. Today* **7**, S107–S112 (2002).
46. Bohannon, J. Animal models. Can a mouse be standardized? *Science* **298**, 2320–2321 (2002).
47. Amsterdam, J. D., Brunswick, D. J. & Hundert, M. A single-site, double-blind, placebo-controlled, dose-ranging study of YKP10A — a putative, new antidepressant. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **26**, 1333–1338 (2002).
48. Feighner, J. P. *et al*. Double-blind, placebo-controlled study of INN 00835 (netamiftide) in the treatment of outpatients with major depression. *Int. Clin. Psychopharmacol.* **16**, 345–352 (2001).
49. Palfreyman, M. G. *et al*. Novel directions in antipsychotic target identification using gene arrays. *Curr. Drug Target CNS Neurol. Disord.* **1**, 227–238 (2002).
50. Suessbrich, H., Waldegger, S., Lang, F. & Busch, A. E. Blockade of HERG channels expressed in *Xenopus* oocytes by the histamine receptor antagonists terfenadine and astemizole. *FEBS Lett.* **385**, 77–80 (1996).
51. Rothman, R. B. *et al*. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* **102**, 2836–2841 (2000).
52. Remington, G. & Kapur, S. SB-277011 GlaxoSmithKline. *Curr. Opin. Investig. Drugs* **2**, 946–949 (2001).
53. Kramer, M. S., Last, B., Getson, A. & Reines, S. A. The effects of a selective D_4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia. D_4 Dopamine Antagonist Group. *Arch. Gen. Psychiatry* **54**, 567 (1997).
54. Gewirtz, G. R. *et al*. BMY14802, a σ receptor ligand for the treatment of schizophrenia. *Neuropsychopharmacology* **10**, 37–40 (1994).
55. Muller, M. J. *et al*. Antipsychotic effects and tolerability of the sigma ligand EMD 57445 (panamesine) and its metabolites in acute schizophrenia: an open clinical trial. *Psychiatry Res.* **89**, 275–280 (1999).
56. van Berckel, B. *et al*. Efficacy and tolerance of D-cycloserine in drug-free schizophrenic patients. *Biol. Psychiatry* **40**, 1298 (1996).
57. Evins, A. E., Amico, E., Posever, T. A., Toker, R. & Goff, D. C. D-Cycloserine added to risperidone in patients with primary negative symptoms of schizophrenia. *Schizophr. Res.* **56**, 19–23 (2002).
58. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* **361**, 799–808 (2003).
59. Stahl, S. M., Entsuah, R. & Rudolph, R. L. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. *Biol. Psychiatry* **52**, 1166–1174 (2002).
60. Perez, V., Gilaberte, I., Faries, D., Alvarez, E. & Artigas, F. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet* **349**, 1594–1597 (1997).
61. Berman, R. M. *et al*. The use of pindolol with fluoxetine in the treatment of major depression: final results from a double-blind, placebo-controlled trial. *Biol. Psychiatry* **45**, 1170–1177 (1999).
62. Nichols, D. E. Hallucinogens. *Parmacol. Ther.* **101**, 131–181 (2004).
63. Kroeze, W. K., Sheffler, D. J. & Roth, B. L. G-protein-coupled receptors at a glance. *J. Cell Sci.* **116**, 4867–4869 (2003).

Acknowledgements

Work in the authors' laboratories is supported by the National Institutes of Health.

Competing interest statement

The authors declare competing financial interests; see Web version for details.

Online links

DATABASES

The following terms in this article are linked online to:
LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/
CREB1

FURTHER INFORMATION

National Institutes of Mental Health Psychoactive Drug Screening Program: http://pdsp.cwru.edu/
PDSP K_i Database: http://kidb.cwru.edu/
Access to this interactive links box is free online.